WHAT IS CLAIMED IS:

1. A method of identifying an anergy modulating agent, comprising:

(a) providing an E3 ubiquitin ligase polypeptide, E3 ubiquitin ligase substrate polypeptide, and a test compound;

(b) contacting the test compound, the ligase polypeptide, and the ligase substrate polypeptide together under conditions that allow the ligase polypeptide to bind or ubiquitinate the substrate polypeptide; and

(c) determining whether the test compound decreases the level of binding or ubiquitination of the substrate polypeptide by the ligase polypeptide, relative to the level in the absence of the test compound, wherein a decrease indicates that the test compound is an anergy modulating agent.

2. The method of claim 1, wherein the ligase polypeptide is selected from the group consisting of: Itch, GRAIL, Cbl, Cbl-b, Cbl-b3, Aip4, and Nedd4.

3. The method of claim 1, wherein the ligase polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12.

4. The method of claim 1, wherein the substrate polypeptide is selected from the group consisting of: PLC-γ, PKCθ, and RasGAP.

5. The method of claim 1, wherein the substrate polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, and SEQ ID NO:18.

6. The method of claim 1, further comprising: (d) determining whether the agent reduces anergy in an immune cell *in vivo* or *in vitro*.

7. The method of claim 1, further comprising: (d) optimizing the pharmacological activity of the agent using modeling software or medicinal chemistry.

8. The method of claim 6, wherein the immune cell is a T cell or B cell.

9. The method of claim 1, wherein the test compound is cell-permeant.

10. The method of claim 1, wherein the ligase polypeptide is Itch and the substrate polypeptide is PLC-γ.

11. The method of claim 1, wherein the ligase polypeptide is Itch and the substrate polypeptide is PKCθ.

12. The method of claim 1, wherein the ligase polypeptide is Aip4 and the substrate polypeptide is PLC-γ.

13. The method of claim 1, wherein the ligase polypeptide is Aip4 and the substrate polypeptide is PKCθ.

14 A process of making an anergy modulating agent, comprising manufacturing the agent identified by the method of claim 1.

15 A method of manufacturing an anergy modulating composition, comprising combining the agent manufactured according to claim 14 with a pharmaceutically acceptable carrier, to thereby manufacture an anergy modulating composition.

16 The method of claim 15, further comprising incorporating the composition into a pharmaceutical composition suitable for administration to an animal via a route selected from the group consisting of oral, parenteral, topical, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac,

intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, and intrasternal.

17. A method of identifying an anergy modulating agent, comprising:

(a) providing a test compound and a polypeptide selected from the group consisting of: Itch, Aip4, GRAIL, Cbl, Cbl-b, Cbl-b3, Nedd4, PLC-γ and PLCθ, or a biologically active fragment thereof;

(b) contacting the test compound and the polypeptide or fragment thereof under conditions that allow the test compound to bind the polypeptide or fragment thereof;

(c) determining whether the test compound binds the polypeptide or fragment thereof; and

(d) determining whether the test compound reduces anergy in an immune cell *in vivo* or *in vitro*, wherein a test compound that reduces anergy is an anergy modulating agent.

18. The method of claim 17, wherein the immune cell is a T cell or B cell.

19. The method of claim 17, further comprising optimizing the pharmaceutical activity of the agent using modeling software or medicinal chemistry.

20. A method of identifying an anergy modulating agent, comprising:

(a) providing a test compound and a polypeptide comprising Itch, Aip4, or a HECT fragment of Itch or Aip4;

(b) contacting the test compound and the polypeptide under conditions that allow the test compound to interact with the polypeptide;

(c) contacting the polypeptide with a reaction mix comprising E1, E2, tagged ubiquitin, and ATP; and

(d) determining whether the test compound prevents the autoubiquitination of the polypeptide in the presence of the reaction mix; wherein a test compound that prevents the autoubiquitination of the polypeptide is an anergy modulating agent.

21. The method of claim 20, further comprising: (e) determining whether the agent reduces anergy in an immune cell in vivo or in vitro.

22. The method of claim 20, wherein the tagged ubiquitin comprises a biotin, epitope, or fluorescent tag.

23. The method of claim 20, wherein the E2 is UbcH7.

24. The method of claim 21, wherein the immune cell is a T cell or B cell.

25. The method of claim 20, further comprising: (e) optimizing the pharmacological activity of the agent using modeling software or medicinal chemistry.

26. A process of manufacturing an anergy modulating agent, the process comprising manufacturing the agent identified by claim 20 to thereby manufacture an anergy modulating agent.

27. A method of manufacturing an anergy modulating composition, the method comprising combining the agent identified by claim 20 with a pharmaceutically acceptable carrier, to thereby manufacture an anergy modulating composition.

28. The method of claim 27, further comprising incorporating the composition into a pharmaceutical composition suitable for administration to an animal via a route selected from the group consisting of oral, parenteral, topical, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and epidural, intrasternal.

29. A method of identifying an anergy modulating agent, the method comprising:

(a) contacting a test compound and an E3 ubiquitin ligase polypeptide under conditions that allow the test compound to interact with the ligase polypeptide;

(b) contacting the ligase polypeptide with a reaction mix comprising E1, E2, tagged ubiquitin, ATP, and an E3 ubiquitin ligase substrate polypeptide; and

(c) determining whether the test compound inhibits the ligase polypeptide from transubiquitinating the substrate polypeptide in the presence of the reaction mix, wherein a test compound that inhibits transubiquitination is an anergy modulating agent.

30. The method of claim 29, wherein the E2 is UbcH7.

31. The method of claim 29, further comprising: (d) determining whether the agent reduces anergy in an immune cell *in vivo* or *in vitro*.

32. The method of claim 29, wherein the immune cell is a T cell or B cell.

33. The method of claim 29, wherein the test compound is cell-permeant.

34. A method of inhibiting anergy in a cell or patient, comprising:

administering to a cell or patient an agent capable of inhibiting the production, activation, activity, or substrate binding ability of an anergy associated E3 ubiquitin ligase, in an amount sufficient to inhibit anergy in the cell or patient.

35. The method of claim 34, wherein the ligase is selected from the group consisting of: Itch, Grail, Cbl, Cbl-b, Cbl-b3, AIP4, and Nedd4.

36. The method of claim 34, wherein the patient is in need of treatment that inhibits anergy in the patient's immune cells.

37. The method of claim 34, wherein the patient is suffering from cancer.

38. The method of claim 37, wherein the agent is administered as a part of a combination therapy for cancer.

39. A method of identifying an agent that inhibits protein-protein interaction between an anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, the method comprising:

(a) providing an E3 ubiquitin ligase polypeptide, E3 ubiquitin ligase substrate polypeptide, and a test compound, wherein the ligase polypeptide or the substrate polypeptide is labeled;

(b) contacting the ligase polypeptide, the substrate polypeptide, and the test compound, with each other; and

(c) determining the amount of label bound to the unlabeled polypeptide, wherein a reduction in the amount of label that binds the unlabeled polypeptide indicates that the test compound is an agent that inhibits protein-protein interaction between an anergy associated E3 ubiquitin ligase and an E3 ubiquitin ligase substrate.

40. A method of identifying an agent that inhibits protein-protein interaction between an anergy associated E3 ubiquitin ligase and an E2 ubiquitin ligase, the method comprising:

(a) providing E3 ubiquitin ligase polypeptide, E2 ubiquitin ligase polypeptide, and a test compound, wherein the E3 ligase polypeptide or the E2 ubiquitin ligase polypeptide is labeled;

(b) contacting E3 ubiquitin ligase polypeptide, the E2 ubiquitin ligase polypeptide, and the test compound with each other; and

(c) determining the amount of label bound to the unlabeled ligase polypeptide, wherein a reduction in the amount of label that binds the unlabeled ligase indicates that the test compound is an agent that inhibits protein-protein interaction between an anergy associated E3 ubiquitin ligase and an E2 ubiquitin ligase.

41. A method for decreasing a protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, the method comprising:

contacting an anergy associated E3 ubiquitin ligase with an agent that decreases an interaction between the anergy associated E3 ubiquitin ligase and an E3

ubiquitin ligase substrate, such that the protein-protein interaction between the ligase and the substrate is decreased.

42. The method of claim 41, wherein the ligase is Itch and the substrate is PLC-γ.

43. The method of claim 41, wherein the ligase is Itch and the substrate is PKCθ.

44. The method of claim 41, wherein the ligase is Aip4 and the substrate is PLC-γ.

45. The method of claim 41, wherein the ligase is Aip4 and the substrate is PKCθ.

46. A method of evaluating a test compound for an ability to modulate anergy, the method comprising:

(a) contacting an immune cell with a test compound; and

(b) determining whether the test compound modulates transcription of at least one anergy associated E3 ubiquitin ligase gene, wherein a test compound that reduces transcription is an anergy modulating agent.

47. The method of claim 46, further comprising: (c) determining whether the agent reduces tolerance induction in T or B cells *in vivo* or *in vitro*.

48. The method of claim 46, wherein the gene encodes a ligase selected from the group consisting of Itch, Grail, Cbl, Cbl-b, Cbl-b3, AIP4, and Nedd4.

49. An agent identified by the method of claim 1, 17, 20, 29, 39, 40, or 46.

50. A vector comprising an isolated nucleic acid molecule encoding an anergy associated polypeptide or biologically active fragment thereof.

51. The vector of claim 50, wherein the anergy associated polypeptide is selected from the group consisting of: Itch, GRAIL, Cbl, Cbl-b, Cbl-b3, Aip4, Nedd4, PLC-γ, PKCθ, and RasGAP.

52. The vector of claim 50, wherein the anergy associated polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, and SEQ ID NO:18.

53. A host cell comprising the vector of claim 49.

54. A host cell comprising an exogenously introduced isolated nucleic acid molecule capable of expressing an anergy associated polypeptide or biologically active fragment thereof.